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A simple and clinically relevant combination of neuroimaging and functional indexes for the identification of those at highest risk of Alzheimer's disease

Hossein Tabatabaei-Jafari*, Erin Walsh, Marnie E. Shaw, Nicolas Cherbuin, For the Alzheimer's Disease Neuroimaging Initiative (ADNI)[1]

Centre for Research on Ageing, Health and Wellbeing, The Australian National University, Canberra, Australia

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ABSTRACT

The current challenge in clinical practice is to identify those with mild cognitive impairment (MCI), who are at greater risk of Alzheimer's disease (AD) conversion in the near future. The aim of this study was to assess a clinically practical new hippocampal index—hippocampal volume normalized by cerebellar volume (hippocampus to cerebellum volume ratio) used alone or in combination with scores on the Mini—Mental State Examination, as a predictor of conversion from MCI to AD. The predictive value of the HCCR was also contrasted to that of the hippocampal volume to intracranial volume ratio. The findings revealed that the performance of the combination of measures was significantly better than that of each measure used individually. The combination of Mini—Mental State Examination and hippocampal volume, normalized by the cerebellum or by intracranial volume, accurately discriminated individuals with MCI who progress to AD within 5 years from other MCI types (stable, reverters) and those with intact cognition (area under receiver operating curve of 0.88 and 0.89, respectively). Normalization by cerebellar volume was as accurate as normalization by intracranial volume with the advantage of being more practical, particularly for serial assessments.

1. Introduction

Mild cognitive impairment (MCI) refers to modest cognitive decline along with preserved daily activities (Association, 2013). Although many people with MCI live largely normal lives, they are at higher risk of developing Alzheimer's disease (AD) than those without MCI (Forlenza et al., 2013). The available evidence suggests that less than half of patients diagnosed with MCI may progress to AD in a 5-year period while the rest remain stable or reverse to cognitively normal (CN) status (Falahati et al., 2014; Pandya et al., 2016). Generally, there is an expectation of eventual conversion from MCI to AD due to the progressive nature of the neurodegenerative processes involved, and MCI stability can depend on the duration of follow-up (Ganguli, 2013). Reversion to CN status is still an unresolved question but may relate to the relatively unspecific nature of diagnostic criteria, interaction with comorbid conditions, and/or variability in the pathological process (Park et al., 2015). Thus, the current clinical challenge is to discriminate individuals with MCI who are more likely to convert to AD.

In their revised position, the National Institute on Aging and the Alzheimer's Association (NIA-AA) considered MCI and AD as different stages of the AD continuum rather than 2 distinct clinical entities (Albert et al., 2011; Jack et al., 2018). In 2011, NIA-AA reviewed diagnostic guidelines and suggested that, owing to greater diagnostic uncertainty earlier in the AD continuum, MCI diagnosis should be supported by biological markers reflecting AD pathology (Albert et al., 2011). In 2018, the NIA-AA work group further qualified this position and recommended that biological markers should reflect neuropathological processes that define the disease instead of simply supporting the diagnosis (Jack et al., 2018). Based on this expert consensus, the work group recommended that AD biomarkers should be incorporated into MCI/AD diagnostic criteria. The NIA-AA work group identified 3 types of AD biomarkers directly related to the underlying pathological processes. The biomarkers include (1) amyloid-β deposition including cortical amyloid positron emission tomography (PET) ligand

* Corresponding author at: Centre for Research on Ageing, Health and Wellbeing, Australian National University, Florey Building 54, Mills Road, Acton, ACT 2601 Australia. Tel.: (612) 61259032; fax: (612) 61251558.
E-mail address: hossein.tabatabaei@anu.edu.au (H. Tabatabaei-Jafari).

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bonding (F^{18}–flutemetamol PET) and low cerebrospinal fluid (CSF) $A\beta_{42}$; (2) aggregated tau including cortical tau PET ligand bonding (flortaucipir-PET) and elevated CSF phosphorylated tau (P-tau); and (3) neurodegeneration or neural injury including PET-detected hypometabolism (fluorodeoxyglucose-PET), CSF total tau (T-tau), and cortical/volume atrophy on magnetic resonance imaging (MRI) scan (Jack et al., 2018).

Much research has been conducted to evaluate amyloid-β deposition, tau aggregation, and hypometabolism using PET scans and CSF biomarkers—separately or in combination—to classify MCI at risk of AD conversion, with some promising performance (Mitchell, 2009; Ritchie et al., 2017; Vandenberghe et al., 2013; Yuan et al., 2009). However, these methods are invasive and, especially for PET imaging, have limited availability in clinical practice. Ideally, a practical biomarker should be widely available, accurate, cost-effective, relatively simple to interpret, easy to use, and be acceptable to patients while not imposing an excessive burden. It is important that—before assessing a new biomarker—clear criteria for selection be established, and the likelihood of meeting them be considered. As a minimum, the proposed new biomarker should perform at least similar to simple, noninvasive, and currently available biomarkers.

A type of noninvasive and more widely available biomarker is provided by structural brain measurement obtained using MRI. Cerebral cortical thickness and hippocampal measures are the most predictive and practical MRI methods to date (Falahati et al., 2014; Rathore et al., 2017). Although cerebral cortical thickness has been shown to be more predictive compared to volumetric measures based on single brain regions, it requires agreement on a standard pattern of cerebral cortical thickness in AD to be adoptable in clinical practice. Hippocampal volume, which has been shown to be a moderate predictor of AD conversion with a sensitivity of 67% and specificity of 72%, has the advantage of being less invasive compared to a CSF biomarker, less costly than a PET scan, and more widely available and clinically easier to use compared to cortical atrophy measures (Chupin et al., 2009). However, using hippocampal volume in the clinical setting is less straightforward compared to the use of this measure in a research setting.

Hippocampal volume needs to be normalized by or adjusted for intracranial volume (ICV) (Whitwell et al., 2001) to control for intersubject (Barnes et al., 2010) and gender (Pintzka et al., 2015) variations in head size, as well as variation in head size estimations in serial scans (Whitwell et al., 2001). The most widely used method in neuroimaging research is adjustment for ICV using its inclusion as a covariate in regression analyses. A less commonly used normalization approach is dividing the hippocampal volume by another volume that can be accurately measured and is not significantly impacted by neurodegenerative processes, typically ICV. In this study, we investigate normalization by cerebellar volume (hippocampus to cerebellar volume ratio) as an alternative approach, to correct for head size/premorbid brain volume as the cerebellum has been shown to be little affected by age-related atrophy in the absence of clinical dementia. Neurodegeneration in AD gradually progresses from the medial temporal lobe to the parietal and frontal lobes and then to the posterior parts of the brain. The cerebellum is among the last brain regions affected by AD pathology (Thal et al., 2002). We have recently shown that cerebellar atrophy is not different in MCI compared to normal aging (Tabatabaei-Jafari et al., 2017). Furthermore, while cerebellar atrophy increases in AD, it remains lower in other regions and particularly in the medial temporal lobe (Tabatabaei-Jafari et al., 2017). Thus, using the cerebellum as a reference area should be both methodologically robust and practical in a clinical context. Importantly, regional brain volume is more accurately measured than ICV using semi-automated methods, such as FreeSurfer (Heinen et al., 2016), and unlike ICV also less affected by field strength (Heinen et al., 2016; Nordenskjold et al., 2013) and segmentation method (Hansen et al., 2015; Keihaninejad et al., 2010; Malone et al., 2015).

Although hippocampal volume is not sufficiently accurate to be clinically useful as a single predictor of MCI who progress to AD, it is a useful benchmark. If other measures sufficiently improve the predictive value of hippocampal volume, they may be worth for further consideration. The Mini–Mental State Examination (MMSE) may be a good candidate. A recent Cochrane review indicated that the weighted sensitivity and specificity of the MMSE for conversion from MCI to AD are 54% and 80% in a limited number of available studies (Arevalo-Rodriguez et al., 2015). Moreover, evidence suggests that a combination of cognitive measures and hippocampal volume can improve the predictive value of hippocampal volume for predicting AD conversion in MCI (Devanand et al., 2008). Therefore, such a combination is also likely to improve on the classification performance of hippocampal volume for identifying MCI who convert to AD in short term from all those who do not convert.

In the present study, we investigated the classification performance of MMSE and hippocampal volume normalized by cerebellar volume or ICV both individually and in combination, to identify individuals with MCI who will convert to AD within 5 years. We expected that these combinations of measures would have classification accuracies high enough to be useful in clinical practice.

2. Methodology

2.1. Study participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by a principal investigator, Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

A total of 1289 participants with MCI (n = 872) or CN (n = 417) at baseline were considered for inclusion. All MCI participants who were stable for at least 6 months after baseline and converted to AD or reverted to CN within 5 years (confirmed with 2 consecutive stable diagnoses) or were stable for at least 5 years were included. Participants who were CN at baseline and were stable throughout the study were also included.

Based on diagnosis and diagnostic change, participants were categorized into 4 groups: (1) MCIc (N = 187), MCI patients who converted to AD in less than 5 years; (2) MCIs (N = 112), MCI patients who were stable for 5 years or more; (3) MCIr (N = 39), MCI patients who reverted to CN in less than 5 years; and (4) CN (N = 322), patients who remained cognitively healthy for the whole follow-up period.

Details of the diagnostic criteria can be found at the ADNI web site (http://www.adni-info.org/Scientists/AboutADNI.aspx). Briefly, participants were classified as CN if they had an MMSE greater than 24, had a clinical dementia rating (CDR) of 0, and did not meet diagnostic criteria for MCI, dementia, or depression. Participants were classified as MCI if they had an MMSE greater than 24, had a CDR of 0.5, had a subjective report of memory concern, had an objective memory loss, had preserved daily living activity, and did not meet diagnostic criteria for dementia. AD participants have MMSE scores less than 26, have a CDR of 0.5 or 1.0, and fulfill criteria for clinically probable AD according to the Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association.

2.2. Neuroimaging acquisition and processing

Participants underwent high-resolution MRI brain scans on 1.5 (N = 335) or 3T (N = 325) scanners from General Electric, Siemens, or Philips (Milwaukee, WI; Germany; the Netherlands, respectively) using a standardized ADNI acquisition protocol for 3D MP-RAGE sequence (Jack et al., 2008). Baseline images that had undergone specific ADNI preprocessing correction steps to standardize images from different sites and platforms were obtained for this study: (1) grad wrap, a specific correction of image geometry distortion due to nonlinearity; (2) B1 nonuniformity, B1 calibration to correct the image intensity nonuniformity that results when RF transmission is performed with a more uniform body coil while reception is performed with a less uniform head coil; and (3) N3 correction, a histogram peak–sharpening algorithm applied after grad wrap and B1 correction. We conducted automatic volumetric segmentation using FreeSurfer (version 5.3, http://surfer.nmr.mgh.harvard.edu/), and the output images were visually checked for the hippocampal and cerebellar segmentations. The criterion was a clear segmentation error assessed by an experienced neuroscientist. Scans with segmentation errors were reprocessed and would only be excluded if the error could not be corrected. In this sample, no image was excluded.

2.3. Measurements

ICV was computed by the sum of the whole brain gray and white matter and CSF volumes. Total cerebellar volume was computed by summing the left and right cerebellar gray and white matter. Total hippocampal volume was the sum of the volumes of the left hippocampus and right hippocampus. Hippocampus to intracranial volume ratio (HCICV) was the ratio of total hippocampal volume to intracranial volume adjusted for age and field strength. Hippocampus to cerebellar volume ratio (HCCR) was the ratio of total hippocampal volume to total cerebellar volume adjusted for age and field strength. No significant correlation was detected between HCICV (correlation = −0.09) or HCCR (correlation = −0.09) and ICV. There was a moderate correlation between hippocampal volume and MMSE (r = 0.35, Supplementary Fig. 1). The residual method was used for all adjustments implemented by running a regression line between raw ratios and the variables using the whole data (Pintzka et al., 2015).

2.4. Statistical analysis

Statistical analyses were performed using the R statistical software (version 3.3.2). Data were checked for missing values and univariate and multivariate outliers using Mahalanobis distance. Discriminant analysis was used to estimate the predictive value of HCICV, HCCR, MMSE, and their combination for clinical status. The DiscriMiner package (version 0.01-29, https://CRAN.R-project.org/package=DiscriMiner) was used for descriptive discrimination and the MASS (version 7.3-45, http://www.stats.ox.ac.uk/pub/MASS4) and Caret package (version 6.3-73, https://CRAN.R-project.org/package=caret) for predictive discrimination (classification). Data were evaluated for normality of all measures (Q-Q plot), linearity, and multicollinearity and singularity (variation inflation factor) assumptions of discriminant analysis, which were all satisfied. Statistically significant heterogeneity of variance-covariance matrices was observed (Box's M-test; $\chi^2 > 51.19$, $p < 0.001$), and therefore, a quadratic classification procedure was used because linear discriminant analysis is known to perform poorly in the presence of heterogeneous covariance matrices (Tabachnick and Fidell, 2013).

For binary classification analyses using quadratic classification procedure, MCIc was contrasted with (1) CN, MCIs, and MCIr pooled together; (2) CN alone; and (3) MCIs and MCIr pooled together and CN was contrasted with MCIs and MCIr pooled together. The stability of the classification procedure was checked by a 10-fold cross-validation. The sample randomly partitioned into 10 equal-size subsamples. Nine subsamples (combined) were used as training data, and the remaining single subsample was retained as the validation data to evaluate predictive model. The process was repeated 10 times, with each of the 10 subsamples used only once as the validation data. The average of the results was provided with confidence interval. We measured reliability using the Kappa coefficient, a chance-corrected measure of agreement between the reference classification (categorized by long-term clinical follow-up) and predictive classification (classifications based on study measures) (Fritz and Wainner, 2001). The receiver operating characteristic (ROC) curve (package pROC version 1.9.1, http://www.biomedcentral.com/1471-2105/12/77/) and the area under the curve (AUC) were used to estimate the discriminant capacity of each model and DeLong's test was used to compare different models (Tabachnick and Fidell, 2013).

3. Results

3.1. Demography and brain measures

The average age of all participants together was 73.76 (SD = 6.80). Participants within the 4 diagnostic groups were similar in age, except for MCIr who were 3 to 5 years younger. *APOE e4* genotype was significantly higher, and MMSE scores were lower in the MCI subgroups than those in the CN group. The average time for MCIc to convert to AD and MCIr to revert to CN was similar at about 2 years. Baseline imaging measures showed that there was a trend of ascending hippocampal volume (adjusted for age, field strength, and ICV), HCICV, and HCCR values in MCIc, MCIs, MCIr, and CN. No such trend was detected for cerebellar volume (Table 1).

3.2. Discriminant analyses; descriptive statistics

Discriminant analyses were conducted to evaluate discriminative performance of the HCICV-MMSE and HCCR-MMSE models. Two discriminant functions were calculated for each model separately. The first function significantly distinguished among the diagnostic groups (HCICV-MMSE: F[6, 1310] = 74.556, HCCR-MMSE: F[6, 1310] = 70.096) and accounted for 99.6% of prediction of MCIc from CN, MCIs, and MCIr (first function's eigenvalue/sum of all eigenvalues × 100) in both models, whereas the second function was not effective in distinguishing CN, MCIs, and MCIr. Predictive values of the combination of HCICV and MMSE or HCCR and MMSE were almost equal (equal standardized coefficient correlation of predictors and discriminant functions) in the first discriminant functions for distinguishing among the groups (Supplementary Table 1).

The binary classification analyses revealed that HCICV, HCCR, and MMSE were equally predictive of MCIc with loadings of more than 0.5 on the discriminant functions (standardized coefficient correlation) with large effect sizes (canonical R^2 and eigenvalue) in all contrasts. In comparison, the standardized coefficients in CN group contrasted with MCIs and MCIr groups were more than 0.5, but because the effect sizes were very low, the discriminant functions were not effective in separating the groups (Supplementary Table 1).

Table 1
Characteristics: demographic information, MMSE, and brain measures. Trends of decrease in the average of MMSE and hippocampal measures are noticeable across the groups.

Diagnostic group	CN	MCIr	MCIs	MCIc	Test of significance ($p < 0.05$)	
Sample size	322	39	112	187	Across groups	Significant pairs
Age; y, mean (SD)	74.55 (5.80)	69.33 (8.32)	72.08 (7.65)	74.31 (7.02)	F (3) = 10.09[a]	CN vs. MCIr CN vs. MCIs MCIc vs. MCIr
Age range, y	59–90	55–87	57–88	55–89		
Male sex; N (%)	158 (49)	17 (44)	72 (64)	113 (60)	χ^2 (3) = 12.68	All pairs are different
Education, y; mean (SD)	16.38 (2.74)	16.87 (2.38)	15.75 (3.03)	16.09 (2.73)	F (3) = 2.285	No difference in pairs
APOE e4; N (%)	82 (25)	19 (49)	40 (36)	127 (68)	χ^2 (3) = 90.63[a]	All pairs are different
One allele	75 (23)	18 (46)	32 (29)	96 (51)		
Two alleles	7 (2)	1 (3)	8 (7)	31 (17)		
Age at DX change, y; mean (SD)	-	71.38 (8.31)	-	76.74 (7.15)	-	MCIc vs. MCIr
Time to DX change, y; mean (SD)	-	2.06 (1.14)	-	2.43 (0.91)	-	-
Measures						
MMSE; mean (SD)	29.08 (1.14)	28.85 (1.23)	28.11 (1.48)	26.95 (1.72)	F (3) = 95.22[a]	MCIc vs. CN MCIs vs. CN MCIr vs. MCIc MCIs vs. MCIc
Hippocampus, mm^3, mean (SD)[b]	7510.06 (807.29)	7210.85 (756.46)	7052.82 (909.03)	6240.78 (888.32)	F (3) = 89.32[a]	MCIc vs. CN MCIc vs. MCIr MCIc vs. MCIs MCIs vs. CN
Cerebellum, mm^3; mean (SD)[b]	121937.60 (9539.73)	120522.40 (9840.47)	121318.00 (10,337.83)	122673.50 (10,510.29)	F (3) = 0.458	No difference in pairs
HCICV; mean (SD)	0.50 (0.06)	0.47 (0.05)	0.46 (0.07)	0.41 (0.06)	F (3) = 87.86[a]	MCIc vs. CN MCIc vs. MCIr MCIc vs. MCIs MCIs vs. CN
HCCR; mean (SD)	6.21(0.73)	5.99 (0.68)	5.85 (0.94)	5.09 (0.79)	F (3) = 79.83[a]	MCIc vs. CN MCIc vs. MCIr MCIc vs. MCIs MCIs vs. CN

Key: APOE e4, apolipoprotein E allele 4; CN, cognitively normal; DX, diagnosis; HCCR, hippocampus to cerebellum volume ratio × 100 adjusted by age and field strength; HCICV, hippocampus to intracranial volume ratio × 100 adjusted by age and field strength; MCIc, mild cognitive impairment converted to Alzheimer's disease in 5 years; MCIr, mild cognitive impairment reverted to normal; MCIs, mild cognitive impairment stable for 5 years or more; MMSE, Mini–Mental State Examination.
[a] Indicates significance at $p < 0.0001$.
[b] Adjusted by age, field strength, and intracranial volume.

3.3. Discriminant analysis; classification

3.3.1. Individual predictor classification

HCICV, HCCR, and MMSE performed similarly in identifying diagnostic groups when tested individually and classified participants of the 4 diagnostic groups into 2 groups: CN and MCIc. A high proportion of CN and MCIc were correctly classified, whereas the majority of MCIs and MCIr were classified as CN and the remainder as MCIc (Table 2).

In binary classifications (Table 3), classification performance of MMSE, HCICV, and HCCR was generally comparable and more specific than sensitive for detecting MCIc from the other 3 groups: classification accuracy from 77.6% to 78.9%, specificity from 90.9% to 92%, and sensitivity from 41.2% to 47.1%. Similar trends were demonstrated in all other contrasts. ROC analyses demonstrated no statistically significant difference between AUC for MMSE, HCICV, and HCCR based on Delong's test in all contrasts (Table 3 and Fig. 1).

Table 2
Group classification performance: predictors separate MCIc from CN but cannot separate MCIs and MCIr from others and majority of them were classified as CN and minority as MCIc

References	MMSE				HCICV				HCCR				HCICV + MMSE				HCCR + MMSE			
	CN	MCIc	MCIs	MCIr	CN	MCIc	MCIs	MCIr	CN	MCIc	MCIs	MCIr	CN	MCIc	MCIs	MCIr	CN	MCIc	MCIs	MCIr
Prediction																				
CN	293	71	76	33	272	70	78	29	283	69	83	34	290	42	75	34	293	43	73	34
MCIc	29	116	36	6	50	117	34	10	39	118	29	5	27	144	37	5	25	142	36	5
MCIs	0	0	0	0	0	0	0	0	0	0	0	0	5	1	0	0	4	2	3	0
MCIr	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sensitivity, %	91.0	62.0	-	-	84.5	62.57	-	-	87.9	63.1	-	-	90.1	77.0	-	-	91.0	75.9	-	-
Specificity, %	46.8	85.0	-	-	47.6	80.13	-	-	45.0	84.6	-	-	55.3	85.4	-	-	55.6	86.1	-	-
Pos Pred Value %	62.0	62.0	-	-	60.6	55.45	-	-	60.3	61.8	-	-	65.8	67.6	-	-	66.1	68.3	-	-
Neg Pred Value %	84.5	85.0	-	-	76.3	84.41	-	-	79.6	85.3	-	-	85.4	90.4	-	-	86.6	90.1	-	-
Prevalence, %	48.8	28.3	17.0	5.9	48.8	28.33	17.0	5.9	48.8	28.3	17.0	5.9	48.8	28.3	17.0	5.9	48.8	28.3	17.0	5.9
Accuracy (95% CI)	62.0 (58.1–65.7)				58.94 (55.1–62.7)				60.8 (56.9–64.5)				65.8 (62.0–69.4)				66.4 (62.6–67.0)			
Kappa, %	33.3				28.90				31.3				41.1				42.1			

Key: 95% CI, 95% confidence interval; CN, cognitively normal; HCCR, hippocampus to cerebellum volume ratio adjusted for age and field strength; HCICV, hippocampus to intracranial volume ratio adjusted for age and field strength; MCIc, mild cognitive impairment converted to Alzheimer's disease in 5 years; MCIr, mild cognitive impairment reverted to normal; MCIs, mild cognitive impairment stable for 5 years or more; MMSE, Mini–Mental State Examination; Neg Pred value, negative predictive value; Pos Pred Value, positive predictive value.

Table 3
Contrast classification performance: MCIc contrasted separately with all 3 groups together, other 2 MCI groups, and CN alone. CN also contrasted with MCIs and MCIr together. In MCIc contrasts (with all groups or CN alone), predictors were mostly specific than being sensitive when they were not in combinations while combinations improved all classification performances.

Measurements	Classification accuracy % (95% CI)	Kappa, %	McNemar test, *p*-value	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	LR^+	LR^-	AUROC (95% CI)
MCIc vs. [CN + MCIs + MCIr]										
MMSE	77.6 (74.2–80.7)	37.5	<0.0001	41.2	92.0	67.0	69.8	5.2	0.6	0.80 (0.76–0.84)
HCICV	78.9(75.6–82.0)	44.0	<0.0001	50.3	90.3	67.1	82.1	5.2	0.6	0.82 (0.79–0.86)
HCCR	78.5 (75.2–81.6)	41.8	<0.0001	47.1	90.9	67.2	81.3	5.2	0.6	0.82 (0.78–0.85)
HCICV + MMSE	83.2 (80.1–86.0)	56.6	0.008	62.6	91.3	74.1	86.1	7.2	0.4	0.89 (0.86–0.91)
HCCR + MMSE	83.5 (80.4–86.2)	57.9	0.0554	65.2	90.7	73.5	86.8	7.0	0.4	0.88 (0.85–0.91)
MCIc vs. CN										
MMSE	80.4 (76.6–83.7)	55.7	<0.0001	62.1	91.0	80.0	80.5	6.9	0.4	0.84 (0.81–0.88)
HCICV	76.4 (72.5–80.1)	48.12	0.0828	62.6	84.5	70.1	79.5	4.0	0.4	0.86 (0.82–0.89)
HCCR	78.8 (75.0–82.3)	52.8	0.0053	63.1	87.9	75.2	80.4	5.2	0.4	0.85 (0.81–0.88)
HCICV + MMSE	85.5 (82.1–88.4)	68.3	0.2010	77.0	90.4	82.3	87.1	8.0	0.3	0.93 (0.90–0.95)
HCCR + MMSE	86.1 (82.7–88.9)	69.4	0.0576	76.5	91.6	84.1	87.0	9.1	0.3	0.92 (0.89–0.94)
MCIc vs. [MCIs + MCIr]										
MMSE	66.6 (61.3–71.6)	33.6	0.0084	62.0	72.2	73.4	60.6	2.2	0.5	0.72 (0.67–0.77)
HCICV	69.2 (64.0–74.1)	36.8	0.0241	78.6	57.6	69.7	68.5	1.9	0.4	0.75 (0.69–0.80)
HCCR	69.8 (64.6–74.7)	38.1	0.0376	78.6	58.9	70.3	69.0	1.9	0.4	0.75 (0.70–0.81)
HCICV + MMSE	74.6 (69.6–79.1)	48.3	0.5898	78.6	69.5	76.2	72.4	2.6	0.3	0.81 (0.76–0.85)
HCCR + MMSE	72.8 (67.7–77.5)	44.9	0.9170	75.9	68.9	75.1	69.8	2.4	0.4	0.80 (0.75–0.85)
CN vs. [MCIs + MCIr]										
MMSE	70.8 (66.5–74.9)	22.2	<0.0001	73.0	58.9	90.7	28.5	1.8	0.5	0.66 (0.61–0.72)
HCICV	69.1 (64.8–73.3)	12.7	<0.0001	93.8	16.6	70.6	55.6	1.1	0.4	0.65 (0.60–0.70)
HCCR	69.3 (65.0–73.5)	11.2	<0.0001	95.7	13.3	70.2	58.8	1.1	0.3	0.61 (0.55–0.66)
HCICV + MMSE	70.4 (66.01–74.5)	20.4	<0.0001	91.0	26.5	72.5	62.0	1.2	0.3	0.70 (0.65–0.75)
HCCR + MMSE	71.7 (67.4–75.7)	23.8	<0.0001	91.9	28.5	73.3	62.3	1.3	0.3	0.68 (0.63–0.73)

Key: 95% CI, 95% confidence interval; AUROC, area under receiver operating characteristic curve; CN, cognitively normal; HCCR, hippocampus to cerebellum volume ratio adjusted for age and field strength; HCICV, hippocampus to intracranial volume ratio adjusted for age and field strength; LR^+, positive likelihood ratio; LR^-, negative likelihood ratio; MCIc, mild cognitive impairment converted to Alzheimer's disease in 5 years; MCIr, mild cognitive impairment reverted to normal; MCIs, mild cognitive impairment stable for 5 years or more; MMSE, Mini–Mental State Examination.

Importantly, using ICV ratio to normalize the hippocampus or using regression to adjust for ICV was separately assessed, which was found to have little impact on the classification results (Supplementary Fig. 2).

3.3.2. Combined predictors classification

The combination of predictors (hippocampal and MMSE) improved almost all aspects of classification performance, but as for individual predictor models, classification was optimal in classifying participants into 2 groups: CN and MCIc. A high proportion of CN and MCIc were correctly classified, whereas a majority of MCIs and MCIr were misclassified as CN and a minority as MCIc (Table 2).

Almost all aspects of classification performance in all binary classifications that identified MCIc from other groups (i.e., MCIc vs. pooled of others, MCIc vs. CN, and MCIc vs. pooled of MCIs and MCIr) were improved with the combination of HCICV or HCCR and MMSE, when compared with the individual predictor. By contrast, combination models did not show improvement in discriminating CN group from pooled MCIs and MCIr groups (Table 3).

The discrimination ability (AUC of ROC analyses) of combinations of HCICV or HCCR and MMSE was significantly better than each predictor individually (Delong's test; $z < -4$, $p < 0.001$), while there was no significant difference between the HCICV-MMSE and HCCR-MMSE models. In addition, analyses suggested that there was no difference in discrimination ability between the combination models and MMSE alone in separating CN group from MCIs and MCIr groups. By contrast, the combination of hippocampal ratios (HCICV or HCCR) and MMSE was significantly better in discriminating MCIc from pooled MCIs and MCIr (Table 3 and Fig. 1). Additional analyses investigating the ability to discriminate MCI who convert within specified time periods (1–5 years) revealed that performance was better in the first 3 years of follow-up compared to the final 2 years (Supplementary Table 2).

Classification performance of the predictors in combination (HCCR-MMSE and HCICV-MMSE), for discriminating MCIc from other groups in all contrasts was generally substantial: classification accuracy for MCIc versus all other groups was more than 83% with sensitivity between 65.2% and 62.6%, with a specificity of 90.7%–91.3% and an AUC of 0.88–0.89. The performance was even better when discriminating MCIc from CN (Table 3).

Based on the partition plots in Fig. 2, individuals with MMSE scores of less than 25 were mostly classified as MCIc regardless of the HCICV and HCCR values. For individuals with higher MMSE values, lower hippocampal ratios were observed in those who were classified as MCIc. For example, for an MMSE score equal to 25, HCICV needed to be less than 0.6% or HCCR less than 7.5%, to be classified as MCIc. The thresholds for HCICV or HCCR were 0.5% and 6.3% for an MMSE of 26, 0.42% and 5.3% for 27, 0.38% and 4.8% for MMSE for 28. HCICV or HCCR needed to be less than 0.35% and 4.3%, respectively, for MCIc diagnosis, when MMSE scores were 29–30. These thresholds were slightly smaller for discriminating MCIc from CN.

4. Discussion

This study aimed to investigate the performance of hippocampal volume normalized to cerebellar volume as a new measure for the clinical discrimination of MCI individuals at risk of AD conversion within 5 years. A combination of HCCR and MMSE was most effective in identifying MCI at risk of conversion. The main findings were that (1) the combination of HCCR or HCICV and MMSE and MMSE performed better in classifying MCI at risk of AD conversion than each measure individually; (2) the classification performance of HCCR and MMSE was similar to that of HCICV and MMSE; and (3) CN and

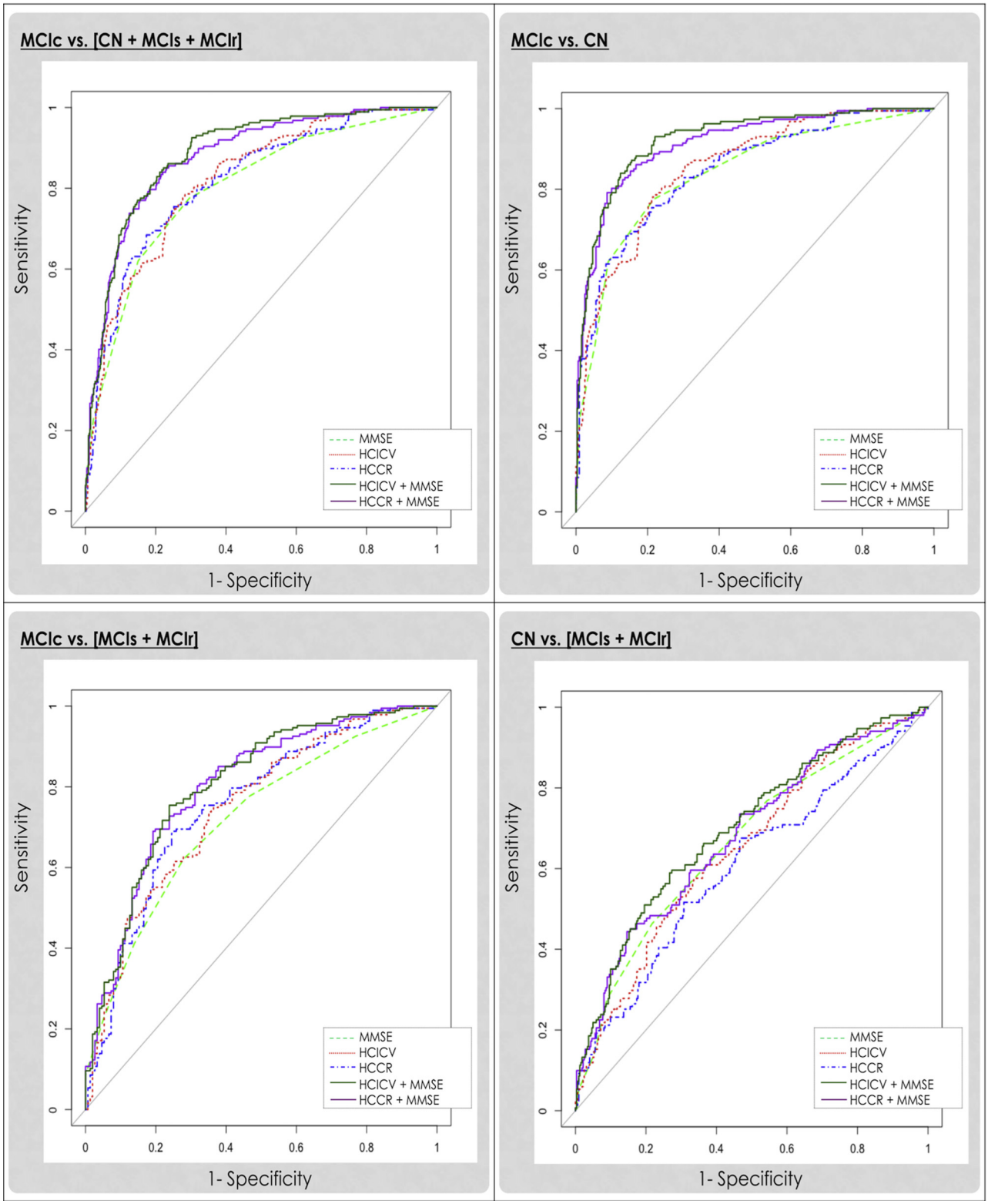

Fig. 1. Receiver operating characteristic (ROC) curve for group membership: Area under the curve (AUC) revealed that in mild cognitive impairment converted to Alzheimer (MCIc) contrasted with pooled of other groups (upper left) or cognitively normal (CN) alone (upper right), combination of Mini–Mental State Examination (MMSE) and hippocampus to intracranial volume ratio (HCICV) or hippocampus to cerebellum volume ratio (HCCR) was better than each predictor separately. This was partially true for MCIc contrasted with pooled of other mild cognitive impairment (MCI) groups (lower left), while not true for CN contrasted with other MCI groups (lower right).

MCI who did not convert to AD within 5 years did not differ statistically in their normalized hippocampal measures at a particular MMSE score.

Among the brain areas implicated in AD neuropathology, hippocampal shrinkage is most predictive of AD-related cognitive dysfunction (Jack et al., 2000), and MMSE is the most widely used

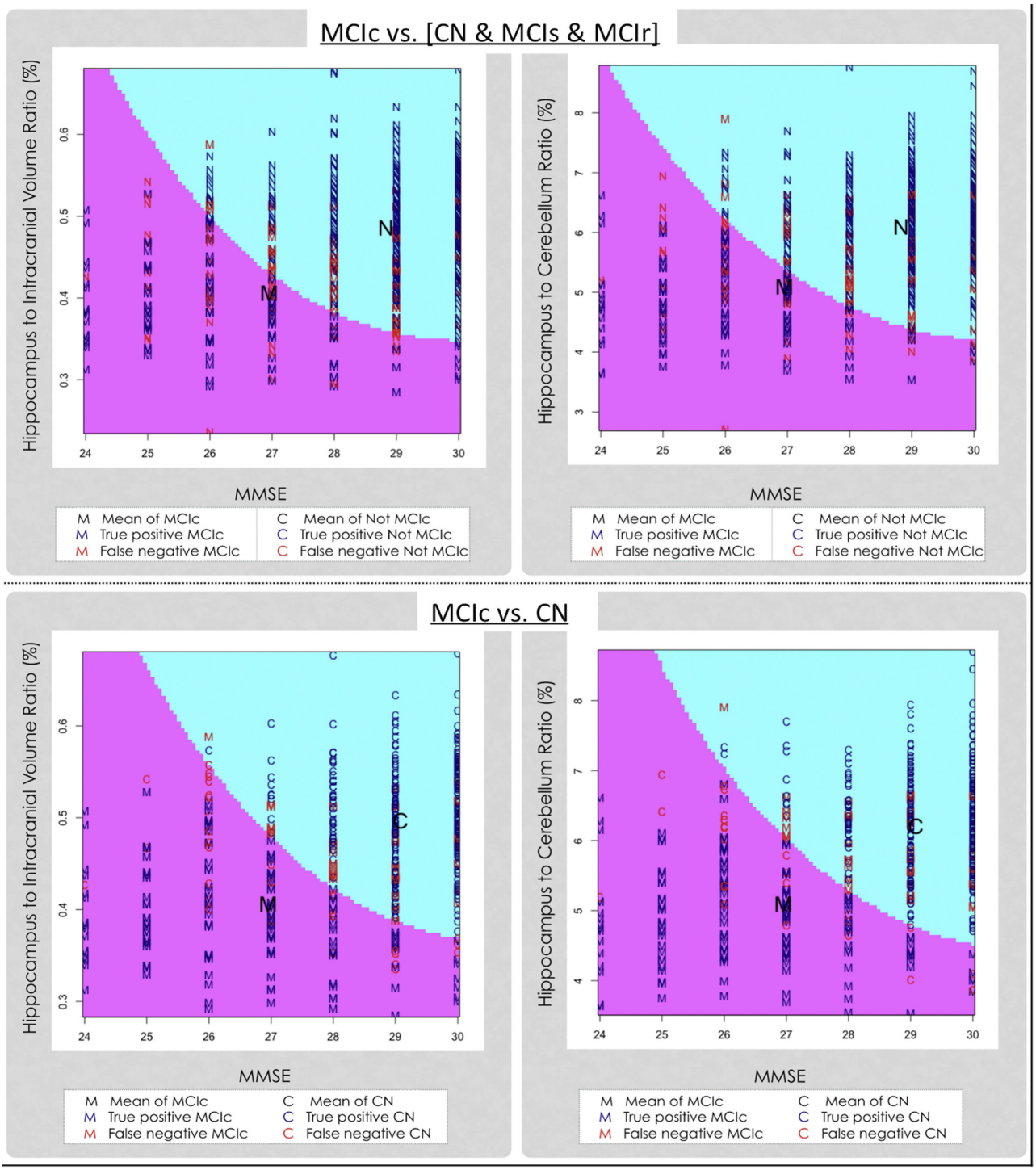

Fig. 2. Partition plots: Thresholds of different hippocampus to intracranial volume (HCICV, right) or hippocampus to cerebellum ratios (HCCR, left) based on different Mini–Mental State Examination (MMSE) scores, which separate mild cognitive impairment converted to Alzheimer (MCIc) from the pooled of cognitively normal (CN) and other mild cognitive impairment (MCI) groups (upper) and from CN alone (lower).

screening instrument for AD/dementia. We found that HCCR, a new normalized hippocampal measure, performed similar to HCICV in classification performance. Although none of HCICV, HCCR, or MMSE reliably identified MCI individuals who progressed to AD alone, we confirmed that HCICV or HCCR in combination with MMSE were effective in differentiating MCI patients who progressed to AD from CN and MCI patients who did not progress.

Both combinations were similar in performance and revealed a high level of classification accuracy, particularly for discriminating between MCIc and CN. However, classification accuracy only reflects the proportion of true results (positive or negative) in the sample. To be practical and useful, a test needs to be sensitive and specific. Our results revealed that of those with MCIc, 65.2%–62.6% were correctly identified (satisfactory sensitivity) by the combination models (HCCR + MMSE or HCICV + MMSE), while 91.3%–90.7%

of nonconverters (CN, MCIs, and MCIr) were correctly identified (high specificity). Furthermore, in those who were positively identified as MCIc, the likelihood of being truly MCIc was about nine-fold that of those who were falsely identified as MCIc (high positive likelihood ratio). For those who were positively identified as MCIc, the likelihood of being MCIc was close to a third that of those who were falsely identified as not having MCIc (low negative likelihood ratio). Therefore, not only was the overall accuracy of the combinations high, but the probabilities of false positive/negative results were also acceptable. Altogether, the combinations of hippocampal measures and MMSE are likely to be better than any single measure in identifying individuals with MCI at risk of AD conversion but also effective in ruling out those individuals unlikely to convert within 5 years.

Interestingly, using either a combination of HCICV and MMSE or HCCR and MMSE resulted in similar performance. This is important because it indicates that normalization of hippocampal volume by ICV or cerebellar volume is equally effective and thus validates our approach. ICV estimation is more sensitive to scanning parameters and segmentation methods than cerebellar volume. This is probably because ICV segmentation relies on the correct identification of the boundary between the subarachnoid space and CSF fluid whose contrast is more variable to that between cerebellar gray matter and CSF. Thus, cross-sectional comparison between patients (or longitudinal within patients) assessed with different scanning parameters may be more difficult when using the ICV ratio. Consequently, in these contexts, normalization by cerebellar volume may be more reliable and preferable.

The classification performance of HCICV and MMSE was in agreement with previous studies (in spite of different study parameters) that revealed a sensitivity of 67% and specificity of 72% for ICV-adjusted hippocampal volume and a sensitivity of 54% and specificity of 80% for MMSE in identifying MCIc from CN (Arevalo-Rodriguez et al., 2015; Chupin et al., 2009). Better performance for the combination models was consistent and comparable with a previous study that showed better prediction of a combination of hippocampal volume, entorhinal cortex volume, MMSE, informant report of functioning questionnaire, the University of Pennsylvania Smell Identification Test, and Selective Reminding Test immediate recall score with a sensitivity of 70% and a specificity of 90% (Devanand et al., 2008). In addition, the models' performances were comparable with other studies with combination of multiple modalities (including MRI and cognitive measures), which mostly had many predictors in each modality (Costafreda et al., 2011; Ferrarini et al., 2009; Moradi et al., 2015; Zhang et al., 2011). This suggests that adding more predictors into a model may not necessarily improve classification performance when the predictors are from a single domain. Therefore, similar to the comparability of the current findings with previous studies that used complex combinations of predictors, the combination of HCCR and MMSE has the advantage of being easily implementable and interpretable and thus may facilitate clinical adoption.

It is interesting to note that MCIs and MCIr did not differ from CN based on the combination of HCICV or HCCR and MMSE while they differed from MCIc. This suggests that those who are not at actual risk of short-term AD conversion are not substantially different from CN. A measure of concurrent decline in function and structure is likely to be a better predictor of AD conversion in short term.

Most classification studies conducted to date were predominantly based on multidomain/multivariate predictors and thus too complex to be easily adoptable in clinical practice. This study stands out in its use of a combination of simple structural (HCCR) and functional (MMSE) measures with a potential diagnostic value for identifying MCI subjects at risk of converting to AD in 5 years easily applicable in clinical practice.

5. Conclusion

The need to evaluate AD-related biological markers for identifying those at risk of AD conversion and to include them in MCI diagnosis has been well documented. However, there is no agreement on a biomarker that can be effectively applied in clinical practice. In the present study, we show that a combination of one brain biomarker, either HCCR or HCICV, and MMSE can accurately identify individuals at risk of AD conversion within 5 years. Moreover, normalization by cerebellar volume is as precise as normalization by intracranial volume with the advantage of being more practical in a clinical setting.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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Authors' contributions: Statistical analysis was carried out by HT-J. TJ contributed to the design of the study, contributed to data management, conducted statistical analyses, and managed all aspects of article preparation and submission. EW contributed to the statistical analysis and article preparation. MES contributed to the image analysis and article preparation. NC contributed to the design of the study, provided methodological input and theoretical expertise, and contributed to writing and editing of the article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2018.05.006.

References

Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B., Phelps, C.H., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement. 7, 270–279.

Arevalo-Rodriguez, I., Smailagic, N., Roque, I.F.M., Ciapponi, A., Sanchez-Perez, E., Giannakou, A., Pedraza, O.L., Bonfill Cosp, X., Cullum, S., 2015. Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst. Rev. CD010783.

Association, T.A.P., 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. Washington, DC.

Barnes, J., Ridgway, G.R., Bartlett, J., Henley, S.M., Lehmann, M., Hobbs, N., Clarkson, M.J., MacManus, D.G., Ourselin, S., Fox, N.C., 2010. Head size, age and gender adjustment in MRI studies: a necessary nuisance? NeuroImage 53, 1244–1255.

Chupin, M., Gerardin, E., Cuingnet, R., Boutet, C., Lemieux, L., Lehericy, S., Benali, H., Garnero, L., Colliot, O. Alzheimer's Disease Neuroimaging, I, 2009. Fully automatic hippocampus segmentation and classification in Alzheimer's disease and mild cognitive impairment applied on data from ADNI. Hippocampus 19, 579–587.

Costafreda, S.G., Dinov, I.D., Tu, Z., Shi, Y., Liu, C.Y., Kloszewska, I., Mecocci, P., Soininen, H., Tsolaki, M., Vellas, B., Wahlund, L.O., Spenger, C., Toga, A.W., Lovestone, S., Simmons, A., 2011. Automated hippocampal shape analysis predicts the onset of dementia in mild cognitive impairment. NeuroImage 56, 212–219.

Devanand, D.P., Liu, X., Tabert, M.H., Pradhaban, G., Cuasay, K., Bell, K., Leon, M.J.D., Doty, R.L., Stern, Y., Pelton, G.H., 2008. Combining early markers strongly predicts conversion from mild cognitive impairment to Alzheimer's disease. Biol. Psychiatry 64, 871–879.

Falahati, F., Westman, E., Simmons, A., 2014. Multivariate data analysis and machine learning in Alzheimer's disease with a focus on structural magnetic resonance imaging. J. Alzheimers Dis. 41, 685–708.

Ferrarini, L., Frisoni, G.B., Pievani, M., Reiber, J.H., Ganzola, R., Milles, J., 2009. Morphological hippocampal markers for automated detection of Alzheimer's disease and mild cognitive impairment converters in magnetic resonance images. J. Alzheimers Dis. 17, 643–659.

Forlenza, O.V., Diniz, B.S., Stella, F., Teixeira, A.L., Gattaz, W.F., 2013. Mild cognitive impairment (part 1): clinical characteristics and predictors of dementia. Rev. Bras. Psiquiatr. 35, 178–185.

Fritz, J.M., Wainner, R.S., 2001. Examining diagnostic tests: an evidence-based perspective. Phys. Ther. 81, 1546–1564.

Ganguli, M., 2013. Can the DSM-5 framework enhance the diagnosis of MCI? Neurology 81, 2045–2050.

Hansen, T.I., Brezova, V., Eikenes, L., Haberg, A., Vangberg, T.R., 2015. How does the accuracy of intracranial volume measurements affect normalized brain volumes? Sample size estimates based on 966 subjects from the HUNT MRI cohort. Am. J. Neuroradiol. 36, 1450–1456.

Heinen, R., Bouvy, W.H., Mendrik, A.M., Viergever, M.A., Biessels, G.J., de Bresser, J., 2016. Robustness of automated methods for brain volume measurements across different MRI field strengths. PLoS One 11, e0165719.

Jack Jr., C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., Holtzman, D.M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J.L., Montine, T., Phelps, C., Rankin, K.P., Rowe, C.C., Scheltens, P., Siemers, E., Snyder, H.M., Sperling, R. Contributors, 2018. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimer's & dementia. J. Alzheimers Assoc. 14, 535–562.

Jack Jr., C.R., Bernstein, M.A., Fox, N.C., Thompson, P., Alexander, G., Harvey, D., Borowski, B., Britson, P.J., L Whitwell, J., Ward, C., Dale, A.M., Felmlee, J.P., Gunter, J.L., Hill, D.L., Killiany, R., Schuff, N., Fox-Bosetti, S., Lin, C., Studholme, C., DeCarli, C.S., Krueger, G., Ward, H.A., Metzger, G.J., Scott, K.T., Mallozzi, R., Blezek, D., Levy, J., Debbins, J.P., Fleisher, A.S., Albert, M., Green, R., Bartzokis, G., Glover, G., Mugler, J., Weiner, M.W., 2008. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. J. Magn. Reson. Imaging 27, 685–691.

Jack Jr., C.R., Petersen, R.C., Xu, Y., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Boeve, B.F., Tangalos, E.G., Kokmen, E., 2000. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. Neurology 55, 484–489.

Keihaninejad, S., Heckemann, R.A., Fagiolo, G., Symms, M.R., Hajnal, J.V., Hammers, A. Alzheimer's Disease Neuroimaging, I, 2010. A robust method to estimate the intracranial volume across MRI field strengths (1.5T and 3T). NeuroImage 50, 1427–1437.

Malone, I.B., Leung, K.K., Clegg, S., Barnes, J., Whitwell, J.L., Ashburner, J., Fox, N.C., Ridgway, G.R., 2015. Accurate automatic estimation of total intracranial volume: a nuisance variable with less nuisance. NeuroImage 104, 366–372.

Mitchell, A.J., 2009. CSF phosphorylated tau in the diagnosis and prognosis of mild cognitive impairment and Alzheimer's disease: a meta-analysis of 51 studies. J. Neurol. Neurosurg. Psychiatry 80, 966–975.

Moradi, E., Pepe, A., Gaser, C., Huttunen, H., Tohka, J. Initiative, A.s.D.N, 2015. Machine learning framework for early MRI-based Alzheimer's conversion prediction in MCI subjects. NeuroImage 104, 398–412.

Nordenskjold, R., Malmberg, F., Larsson, E.M., Simmons, A., Brooks, S.J., Lind, L., Ahlstrom, H., Johansson, L., Kullberg, J., 2013. Intracranial volume estimated with commonly used methods could introduce bias in studies including brain volume measurements. NeuroImage 83, 355–360.

Pandya, S.Y., Clem, M.A., Silva, L.M., Woon, F.L., 2016. Does mild cognitive impairment always lead to dementia? A review. J. Neurol. Sci. 369, 57–62.

Park, M.H., Han, C. Initiative, t.A.s.D.N, 2015. Is there an MCI reversion to cognitively normal? Analysis of Alzheimer's disease biomarkers profiles. Int. Psychiatry 27, 429–437.

Pintzka, C.W., Hansen, T.I., Evensmoen, H.R., Haberg, A.K., 2015. Marked effects of intracranial volume correction methods on sex differences in neuroanatomical structures: a HUNT MRI study. Front. Neurosci. 9, 238.

Rathore, S., Habes, M., Iftikhar, M.A., Shacklett, A., Davatzikos, C., 2017. A review on neuroimaging-based classification studies and associated feature extraction methods for Alzheimer's disease and its prodromal stages. NeuroImage 155, 530–548.

Ritchie, C., Smailagic, N., Noel-Storr, A.H., Ukoumunne, O., Ladds, E.C., Martin, S., 2017. CSF tau and the CSF tau/ABeta ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst. Rev. CD010803.

Tabachnick, B.G., Fidell, L.S., 2013. Using Multivariate Statistics, sixth ed. Pearson, London, UK.

Tabatabaei-Jafari, H., Walsh, E., Shaw, M.E., Cherbuin, N. Alzheimer's Disease Neuroimaging, I, 2017. The cerebellum shrinks faster than normal ageing in Alzheimer's disease but not in mild cognitive impairment. Hum. Brain Mapp. 38, 3141–3150.

Thal, D.R., Rub, U., Orantes, M., Braak, H., 2002. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology 58, 1791–1800.

Vandenberghe, R., Nelissen, N., Salmon, E., Ivanoiu, A., Hasselbalch, S., Andersen, A., Korner, A., Minthon, L., Brooks, D.J., Van Laere, K., Dupont, P., 2013. Binary classification of (1)(8)F-flutemetamol PET using machine learning: comparison with visual reads and structural MRI. NeuroImage 64, 517–525.

Whitwell, J.L., Crum, W.R., Watt, H.C., Fox, N.C., 2001. Normalization of cerebral volumes by use of intracranial volume: Implications for longitudinal quantitative MR imaging. Am. J. Neuroradiol. 22, 1483–1489.

Yuan, Y., Gu, Z.X., Wei, W.S., 2009. Fluorodeoxyglucose-positron-emission tomography, single-photon emission tomography, and structural MR imaging for prediction of rapid conversion to Alzheimer disease in patients with mild cognitive impairment: a meta-analysis. Am. J. Neuroradiol. 30, 404–410.

Zhang, D., Wang, Y., Zhou, L., Yuan, H., Shen, D. Alzheimer's Disease Neuroimaging, I., 2011. Multimodal classification of Alzheimer's disease and mild cognitive impairment. NeuroImage 55 (3), 856–867.